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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,501	12/17/2001	Guido Henning	Le A 35 012	4394

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EXAMINER	
WALLENHORST, MAUREEN	
ART UNIT	PAPER NUMBER
1743	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/023,501	HENNING ET AL.	
	Examiner	Art Unit	
	Maureen M. Wallenhorst	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-10* is/are rejected.

7)☒ Claim(s) *1-5 and 7-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 23, 2007 has been entered.

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

3. Claims 1-5 and 7-10 are objected to because of the following informalities: In part c) of claim 1, the phrase "within a constituent region of a of said tissue sample" does not make proper sense. Appropriate correction is required.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-2, 4-5 and 8-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 and 4 of copending Application No. 10/022,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are broader than those of the 10/022,618 application in that the instant claims recite cancer cells and their precursors, whereas the claims of the '618 application recite cancer cells and their precursors "in uterine cervical smears". The instant claims are broader than the claims of the '618 application and are thus anticipated by the '618 application. See In re Goodman.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 5 and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Rao et al (see the journal articles entitled "Single Cell Multiple Biomarker Analysis in Archival Breast Fine-Needle Aspiration Specimens: Quantitative Fluorescence Image Analysis of DNA

Content, p53 and G-actin as Breast Cancer Biomarkers", submitted in the IDS filed on July 8, 2002).

Rao et al teach of a method for evaluating breast legions for cancerous cells. The method of Rao et al involves staining markers such as p53, G-actin and DNA content in breast legion samples with a stain. In the abstract of the article, Rao et al specifically teach QF image analysis of multiple biomarkers (p53, G-actin and DNA content) on a single cell basis. With respect to the staining, Rao et al teach at page 1028 that immunofluorescent labeling takes place by using a Code-On automatic stainer. Page 1030 further describes the staining as distinctive in that G-actin stains more intensively in cytoplasm, whereas p53 is slightly stronger in the nuclei of tumor cells. After staining, the samples are scanned by an automated image analysis system and biomarkers are detected. Cellular portions of the samples are imaged and measured, and the values are automatically stored in a database. See page 1028. The data is analyzed quantitatively and qualitatively, and the results are converted into positive-negative schema. The data analyses are carried out using a software program (i.e. Microsoft Excel program). The image analysis system is considered to be an automatic information processing system that is linked to a diagnostic expert system. The software program taught by Rao et al is taken to be a diagnostic expert system because of its ability to convert the quantitative values into positive-negative schema (i.e. convert the data into a diagnosis of a disease state). See pages 1028 and 1030 of Rao et al. Rao et al further performed the method using multiple markers, such as the combination of G-actin and DNA content. The article states that none of the benign cases were positive for G-actin and DNA simultaneously, and that none of the cancer cases were negative for G-actin and DNA content simultaneously. Thus, the measurement of the two biomarkers

took place simultaneously as a mixture of biomarkers. The article teaches that using multiple markers provides a powerful tool for breast cancer detection. See page 1031. With respect to claim 5, Rao et al's teaching of the detection of cancerous cells in breast legions meets the limitation of detecting tumors in the mammary gland.

9. Claims 1, 3-5, 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by McNamara et al.

McNamara et al teach of a method for analyzing cells for the detection of cancerous cells, such as those found in breast cancer, ovarian and/or endometrial cancer and prostate cancer. The method of McNamara et al involves staining a cell sample with multiple stains including immunohistochemical, histological and DNA ploidy stains. Each immunohistochemical stain is coupled with a primary antibody known to bind with their respective cytological markers and is used in the diagnosis of diseases, such as cancer. Specifically, McNamara et al teach antibodies to p53, Her-2/neu, EGFR, Ki-67 and Bcl-2 (see col. 40, lines 25-67). For breast cancer, McNamara et al teach using PR, Her-2/neu, p53, CD31 and Ki-67. For prostate cancer, McNamara et al teach using Ki-67, CD31 and p53 (see col. 41, lines 28-40). At col. 41, lines 55-64, McNamara et al teach that a clinician can simultaneously detect multiple cytological markers (p53, Her-2/neu, Ki-67) allowing a more accurate diagnosis. After staining of the samples, spectral imaging is performed and the data is collected using a SPECRTACUBE™ (col. 36, line 64-col. 37, line 23). In analyzing the results of the data collected, McNamara et al teach using spectral and spatial data. The spectral data is displayed as a useful image for the user. The spatial-spectral correlation of the spectrum image provides data about various types of cells that

may appear similar to the naked eye. Thus, in addition to the image data, the cells can also be differentiated.

10. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Bacus et al (US Patent no. 5,109,429).

Bacus et al teach of a kit for analyzing biological specimens for cancer diagnosis and/or prognosis. The kit of Bacus et al comprises slides, one or more bottles of staining reagent, auxiliary agents, such as sulfonating agents and buffers, instructions for the operator and a reference area for calibration. Bacus et al teach that the kit provides an easy and inexpensive means for detecting minute alterations in specimen cells. See the claims in Bacus et al. Since the kit taught by Bacus et al contains all of the physical components recited in instant claim 7, the kit taught by Bacus et al would inherently be able to perform the method according to instant claim 1. Kit claims are patentable based upon the physical components that make up the kit, not upon an intended method or function to be performed by the components of the kit.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Rao et al or McNamara et al in view of Bacus et al (US Patent no. 5,109,429). For a teaching of Rao et al, McNamara et al and Bacus et al, see previous paragraphs in this Office action.

The disclosures of both Rao et al and McNamara et al fail to teach of a kit having the necessary reagents therein for carrying out the method for detecting cancerous cells.

Based upon the combination of either Rao et al or McNamara et al and Bacus et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the components needed to carry out the methods taught by Rao et al and McNamara et al into a kit so as to allow a user to have all of the supplies needed for the easy detection of cancer cells in a convenient package.

14. Applicant's arguments filed April 23, 2007 have been fully considered but they are not persuasive.

The previous rejection of the claims under 35 USC 112, second paragraph made in the last Office action mailed on August 22, 2006 has been withdrawn in view of Applicants' amendments to the claims. The previous rejection made under the ground of obviousness-type double patenting is maintained since Applicants have not filed a terminal disclaimer over application serial no. 10/022,618.

Applicants argue the rejection of the claims under 35 USC 102(b) as being anticipated by Rao et al by stating that Rao et al fail to teach of detecting multiple markers within a single cell or within a constituent region of a tissue section, and fail to teach of combining and accrediting

the signal intensities detected and comparing them to a threshold value to indicate the presence of cancer cells or their precursors. Applicants argue that Rao et al measures the signal intensity over a whole slide, and that in Rao et al, some samples that are non-cancerous are positive in two markers, whereas some cancer samples are positive for only one marker. In response to these arguments, it is noted that Rao et al clearly teach "the biomarkers p53, G-action and DNA content are labeled with an immunofluorescence technique and measured by quantitative fluorescence image analysis (QFIA) simultaneously on a single cell basis". See the abstract and the last paragraph in the right hand column on page 1028 of Rao et al. Rao et al also teach that the technique of QFIA allows the labeling and measurement of cells to be performed in situ (i.e. in the natural state) without the need to remove the cells from the slide. This in situ analysis of the cells allows the morphology of the cells to be preserved. Rao et al also teach in the section entitled "QFIA for Biomarkers" in the right hand column on page 1028 that "G-actin and p53, cytoplasmic and nuclear gray value **for each cell** were measured separately... The corresponding values of G-actin, DNA and p53 **for each cell** were automatically stored in the database". Therefore, contrary to Applicants' argument, Rao et al do teach that multiple markers within a single cell are measured.

In further response to Applicants' arguments, it is noted that Rao et al do teach that the three markers G-actin, p53 and DNA content are simultaneously measured using the QFIA image analysis system. This analysis system serves to analyze and combine all of the signal intensities for each of the markers simultaneously as in the instant invention. The combined signal intensities are compared to different threshold values for each of the markers G-actin, DNA content and p53. See the bottom of page 1029 in Rao et al that describes the threshold

values for the markers. With regards to some of the non-cancerous and cancerous samples listed in Table 1 of Rao et al, it is noted that the abstract in Rao et al clearly states that the results of testing show that none of the benign cases were positive for G-actin and DNA content simultaneously, and none of the malignant cases were negative for both G-actin and DNA content together. Therefore, the combination of both of these markers simultaneously is needed in order to make either a positive or negative diagnosis.

Applicants argue the rejection of the claims under 35 USC 102(b) as being anticipated by McNamara et al by stating that McNamara et al fail to teach of detecting multiple markers within a single cell or within a constituent region of a tissue section, and fail to teach of combining and accrediting the signal intensities detected, and comparing the combined intensities to a threshold value to indicate the presence of cancer cells or their precursors in a cell sample or tissue sample. In response to this argument, it is noted that McNamara et al do teach of detecting multiple markers within a single cell since in the method disclosed by McNamara et al, a biological sample containing cells is combined with multiple stains that serve to stain different markers in cells such as DNA or various immunochemical antigens on the cells. McNamara et al teach that the method involves the in situ analysis of "cellular or tissue components situated and preferably fixated in their natural place or position within the cell or tissue". See lines 6-10 in column 36 of McNamara et al. In addition, McNamara et al teach that "the sample may be a smear of individual cells or a tissue section". See lines 21-22 in column 36 of McNamara et al. McNamara et al also teach that a spectral data collection device serves to detect light intensity associated with distinct spectral bands in separate spatial elements or pixels of the examined sample. The spectrum of light emitted by every point of a sample placed in the field of view of

the spectral data collection device is analyzed. See lines 63-67 in column 36 and lines 1-10 in column 37 of McNamara et al. Therefore, if each separate spatial pixel of a sample placed before the spectral data collection device is analyzed, then individual cells or constituent sections of a tissue sample located in the separate spatial pixels are examined for staining with the multiple individual stains.

In further response to Applicants' arguments, McNamara et al do teach of combining and accrediting all of the signal intensities from each stain used since an overlapping image of all the staining intensities from each of the markers used by McNamara et al is obtained. In addition, McNamara et al teach that control or calibration samples are stained in the same manner and with the same stains as the test biological samples. The staining results provided by the control/calibration samples provide threshold levels with which to compare the staining results of the test biological samples. See lines 20-23 in column 38 of McNamara et al.

For all of the above reasons, Applicants' arguments are not found persuasive.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 571-272-1266. The examiner can normally be reached on Monday-Thursday from 6:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 7, 2007

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